REMARKS

Claims 23-26, 28, 30-33, 35, and 40-44 are currently under consideration. Claims 1-22, 27, 29, 34, and 36-39 have been cancelled. In the last Office Action, prosecution was re-opened after a brief on appeal was filed. The Applicants have elected to respond to the Office Action. The Claims have been amended for the purpose of expediting prosecution. In view of the Examiner's refusal to accept any of the Declarations or other evidence offered by the Applicants, all such evidence is hereby withdrawn from the case.

This case is a Division of USPN 6,420,176, which was drawn to a novel DNA complex for gene delivery. The present set of Claims contains only one independent claim, drawn to a needleless method of transfecting antigen presenting cells of the skin or mucosa of an animal using the novel DNA complex and other materials.

The Claims have been amended as suggested by the Examiner. The amendments to Claim 23 are supported at least at original Claims 8-10, Example 6 and Example 8 (sugar or polyethylenimine or polyehtylenimine derivative) and the Abstract (without the use of a needle). Claim 43 has been amended to correct a typographic error.

1. Written Description

A. Claims 23-26, 28, 35 and 37-39 - "one or more compounds"

The Examiner has objected to the use of the phrase "one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives" in claim 23 under 35 USC § 112 as lacking written description, but has admitted that each of the individual types of materials is supported. Accordingly, Claim 23 has been amended to individually recite the materials.

This application discloses the use of DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6 at page 21 line 15, Table 1), and DNA alone, DNA in combination with PEI, and DNA in combination with PEI modified with mannose, each combined with a sugar (formulated in glucose solution, Experiment 8, page 22, line 35 , Table 2) *in the experiments.*

2. Enablement – Claims 37-39

Although the method described in Claims 23-26, 28, 30-33, 35 and 40-43 is admittedly enabled, dependent Claims 37-39 remain rejected because, it is said, the cells transfected according to the method may not induce a therapeutic or prophylactic immune response. Accordingly, the Claims have been cancelled without prejudice.

3. Indefiniteness – Claims 23, 30 and 31

Claim 23 is said not to have a preamble agreeing with the body of the claim, and the claim has been amended as suggested by the examiner.

Claim 23 is said to be defective because the term "applying" is said to include injection. Accordingly, the Claims have been amended to recite that the claimed method is application without the use of a needle. This amendment is supported at least at page 25, line 14.

Claim 23 is said to be defective because "gene delivery complex that targets antigen presenting cells" is said to be indefinite. Accordingly, the Applicants have amended the claim to recite that the gene delivery complex transfects antigen presenting cells, which is admittedly enabled and in agreement with the preamble.

Claim 30 is said to be indefinite. Accordingly, Claim 30 has been amended to depend from Claim 26, and also recite that the derivative is mannosylated polyethylenimine. Claim 44 is added, and Claim 42 is amended to depend from it.

Claim 31 is said to be indefinite because the phrase "is formulated in a glucose solution" is unclear. Accordingly the Claim has been amended to recite that the complex is "added to" a glucose solution.

Claims 38 and 39 are rejected as indefinite because the Claims are said not to further limit Claim 37. Accordingly, the claims have been amended to depend from Claim 23, and to further narrow the scope of the claimed DNA sequence.

4. Anticipation – Claims 23-26, 28, 30-32, 37, 40, 41 and 43 - Behr

Claims 23-26, 28, 30-32, 35, 37, 40 41 and 43 remain rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240) as supported by Carson (US Patent 5,679,647) Mittal and Kuby.

The Examiner has stated that the previous rejection did not give the language added to the present Claims "whereby antigen presenting cells of said skin or mucosa are transfected" patentable weight. Accordingly, the present rejection is inapplicable to the amended Claims.

5. Obviousness – Claims 23-26, 28, 30-32, 37, 40, 41 and 43

Claims 23-26, 28, 30-32, 35, 37-41 and 43 rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240) as supported by Carson (US Patent 5,679,647), newly added references Mittal and Kuby and in view of Holler (US Patent 5,908,923). To the extent that the prior rejection is being considered, the Applicants offer the following comments. In brief, the amended Claims are not subject to the present rejection because, among other things, the phrase "whereby antigen presenting cells of said skin or mucosa are transfected" must be given patentable weight.

A. The present Invention

The present inventions relates to a method of transfecting antigen presenting cells, the steps comprising selecting a gene delivery complex that transfects antigen presenting cells, comprising DNA and a sugar, or polyethylenimine, or polyethylenimine derivative, and administering the complex by applying the complex without the use of a needle to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, and whereby antigen presenting cells of said skin or mucosa are transfected.

An advantage enjoyed by this invention is that the gene delivery complex need not be injected, but merely applied without the use of a needle to the skin, according to the claimed method. The inventors have found, and the text of the application discusses, methods of stimulating the immune system by administering DNA plus mannosylated PEI, DNA plus modified PEI, PEI with sugars, PEI alone, and sugars alone) without needles, added irritants or toxins, the use of cultured cells or expensive equipment such as a gene gun.

B. The Prior Art

The Behr Reference

The Behr reference teaches only direct injection into the brain for the transfection of neural tissue. The Behr reference does not show transfection of any antigen presenting cells of the skin; indeed the methods described in the Behr reference bypass the skin entirely.

Generally, the Behr reference relates to the use of PEI as an adjuvant for gene therapy (Abstract), preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from the subject matter of the present invention, which is immunotherapy, and the reference discloses that immunogenicity (i.e., raising an immune response) is to be avoided (Col. 1, line 51).

One distinction that can be made between the two classes of endeavor is the type of cells that are transfected. The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), but it does not disclose or discuss the transfection of antigen presenting cells. This makes sense because antigen presenting cells give rise to immune responses, that is, immunogenicity, a result that is not desired for the purposes of the Behr reference. It discusses the use of a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57) but does not discuss or disclose the use of such targeting elements for the purpose of transfecting antigen presenting cells; sugars are listed as useful for targeting the asialoglycoprotein receptors at Col 5, lines 64-65), not the mannose receptor of the present set of amended claims. There is disclosure that topical formulations may be made along with every other known kind, ("cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4)) but again, there is no disclosure or discussion of how such a preparation might be made or might be used to transfect antigen presenting cells. The implication, of course, is that the topical application would be used for gene therapy purposes, and not for generating undesired immunity. Both saline (Example 13 and glucose Example 14) formulations are disclosed, without any distinction as to any advantage that might be obtained. Only direct injection into the brain for the transfection of neural tissue is shown in any experiments, and

there is no disclosure of how to accomplish gene delivery by means of topical administration without the use of needles, or any disclosure whatsoever of the transfection of antigen presenting cells of the skin.

The present invention is directed to the transfection of a class of cells that is prominent by omission from the Behr reference, for good reason: the present invention results in what is for the Behr references' purpose, an undesired response.

The Carson Reference

The Carson reference has been said to provide a reasonable expectation of success if one were to use the Behr materials in the previously claimed method. However, the Behr reference itself undercuts this position because the materials of the Carson reference were used in two experiments from the Behr reference, and found not to work. The Carson reference used plasmid DNA only, and is referred to repeatedly as "naked" defined as "not complexed." Col. 5, line 13. This material was formulated in saline solution (Col. 31, line 18). Both of the cited experiments rely on devices: intradermal injection of plasmid (Example X, column 35, line 48) or a tyne device (Col. 37, line 16), that is, needles. Naked DNA formulated in a glucose solution was tested in the Behr reference Example 14, Col. 13, lines 9-10, injected and found not to work in that experiment. Similar results were obtained in an in vitro experiment using saline solution in the Behr reference at Example 13, Col. 12, lines 39-41). Thus the Carson reference is only useful as a disclosure of a raw material that has not yet been made to work.

The Holler Reference

USPN 5,908,923 to Holler, et al. discloses and claims a sequence listing for a specific transdominant negative integrase gene which is said to be capable of making at least one cell resistant to a retroviral infection. This gene was used *in vitro* to transfect a lymphoblastoid cell line, that is a cancer cell line, neither an antigen presenting cell nor an antigen presenting cell of the skin. The Examiner admits that this reference does not disclose any *in vivo* method. Because method limitations are missing from both the other references, this one cannot fill that gap.

C. Analysis

To the extent the last rejection might be applied to the present claims, the Applicants note that the prior rejection did not give patentable weight to the added limitations that are currently presented. None of the references, separately or in combination disclose how to modify the teachings of the Behr reference to obtain the claimed method of transfecting antigen presenting cells of the skin, the steps comprising selecting a gene delivery complex that transfects antigen presenting cells, comprising DNA and a sugar, or polyethylenimine, or polyethylenimine derivative, and administering the complex by applying the complex without the use of a needle to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, and whereby antigen presenting cells of said skin or mucosa are transfected.

The transfected APC are capable of producing a CTL response (page 11, line 21), which is toxic for the purposes of the Behr reference (Col. 1, line 51). In order for this rejection to stand, there must be some clear teaching as to how to modify the Behr reference, without undercutting its fundamental purpose. Such teaching is found only in the present application, not in the references.

The disclosure of the Behr reference cannot be extended to the transfection to every other class of cell, or the claimed needleless method. The present application discloses that an article published several years after the Carson and Holler references compared transfection rates in antigen presenting cells and a cancer cell line (melanoma) that was known to be readily transfected by all the methods tested. (page 21, lines 2-4). This article reported only "low efficient" *in vitro* methods were known at the time, see page 6, lines 4-11 (cite to Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997 and Song, E. S., et al., PNAS USA 94:5, 1943-8, 1997); and that neither they nor the known *in vivo* methods had been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin into the Langerhans cells. See page 6, lines 16-19. Thus, these references do not add any new teaching to the disclosure of the Behr reference.

None of the secondary or tertiary references provide the elements missing from the claimed method, or any of the missing teachings.

In view of the above analysis and the evidence, it is respectfully submitted that the present rejection is inapplicable to the amended claims because neither the individual references nor their combination yield the claimed invention.

6. Double Patenting

The claims of the present application have been provisionally rejected as being unpatentable over the claims of copending application No. 08/803484 in view of the disclosure of '484. The claims are admitted to be nonidentical, and neither set of claims has been allowed. The Examiner states that the basis for this rejection is that, if various limitations in the claims from one application or the other are ignored, the distinction between the applications would be blurred. It is requested that this issue be held in abeyance until the claims have been allowed.

CONCLUSION

For all the above reasons and amendments, it is believed that all the Examiner's legitimate concerns have been fairly met. Favorable consideration is solicited.

Respectfully Submitted,

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